REMARKS/ARGUMENTS

Pending Claims:
Claims 47-56, 58-61, and 63 have been cancelled. New claims 64-74 have been added. The claims have been amended to clarify the invention and to more clearly recite the claim elements in active steps. No new matter has been added by this amendment, nor has any subject matter been relinquished as a result of this amendment.

Examiner's Objections to the Claims:
The Examiner's objections to the informalities of claims 47, 48, 51, and 63 are rendered moot by Applicant's claim amendment.

Examiner's Enablement Rejections:
The Examiner rejected the prior pending claims 47-56, 58-61, and 63 as not enabled by the specification. The Examiner's rejection is premised on the scope of the claimed method encompassing "gene therapy". To the extent this rejection is maintained for the amended claims, Applicants respectfully traverse.

Applicants' claims are directed to methods for the delivery of a gene to a target cell using retroviral vectors produced *in situ*. As described in the specification, including working examples, Applicant's have surprisingly discovered that a subject's cell can be transduced with nucleic acid sequences suitable for producing a replication-defective retroviral particle harboring a heterologous gene. On expression and release of the retroviral particle in the transduced subject's cells, neighboring cells are infected with the replication-defective virus, thereby delivering the heterologous gene to the neighboring cells via virus-mediated delivery.

Applicants' again assert that the claimed method does not purport to achieve medical cures by gene therapy, but does seek to deliver a gene of interest to cells in living tissues. It is irrelevant to the claimed method if the delivered genes produce a therapeutic effect, although such therapy is not excluded. The effective use of the claimed method is in the successful delivery of a gene, not in the gene's therapeutic value. That the claimed method may be useful in delivering therapeutic genes for gene therapy does not, without more, prevent patentability. Accordingly, the claims are fully enabled and described by the specification. No higher standard is required. Removal of this rejection is requested.

Further, the Examiner's enablement rejection is based on the suggested unpredictability of gene therapy, citing review articles from 1997, 1998, and 2000. Applicants respectfully point to U.S. Patent No. 6,503,501, issued January 7, 2003, and numerous other publications and reports of clinical trials that, contrary to the Examiner's position, demonstrate successful transfer of genes of interest to human patients. These clinical trials also demonstrate improvements in patient outcome, measured by improved clinical parameters, after transfer of a variety of different genes. See, for example, the clinical

trial summaries produced at the *Journal of Gene Medicine*'s website, www.wiley.co.uk/genetherapy/clinical/. Paper copies of these gene therapy clinical trial summaries are attached for the Examiner's consideration.

Also attached are reports of successful gene transfer to human patients demonstrating improved clinical outcomes. See, for example:

Disease	DNA Vector	Citation
stage IV melanomas	liposome	Nabel et al., 1993, *PNAS*, 90:11307-11311
hepatocellular carcinoma	direct DNA injection	Habib et al., 1996, *CancerDetect.Prev.*, 20:103-107
cystic fibrosis	cationic liposome into nasal epithelial cells	Caplen et al., 1995, *Nat. Med.*, 1:39-46; Porteous et al., 1997, *Gene Ther.*, 4:210-218
hypercholesterolemia	retroviral transduced hepatocytes	Raper et al., 1997, *Ann. Surg.* 225:442-443
SCID-X1	retroviral transduced bone marrow cells	Onovera et al., 1998, *Blood* 91:30-36
advanced squamous cell carcinoma	liposome transduced tumor cells	Gleich et al., *Arch. Otolaryngol. Head Neck Surg.*, 124:1097-1104
cervical and ovarian cancer	liposome injections	Hui et al, 1997, *Gene Ther.*, 4:783-790
α1-antitrpypsin deficiency	liposome transduced nasal epithelial cells	Brigham et al., 2000, *Hum. Gene. Ther.*, 11:1023-1032
preventing restinosis and myocardial ischemia following angioplasty	catheter-mediated gene delivery to coronary arteries	Laitinen et al, *Hum. Gene Ther.*, 11:263-270
inoperable angina pectoris	direct DNA injection into cardiac tissue	Sylven et al., 2001 *Coronary Artery Disease* 12:239-243

Each of the references discussed above demonstrates successful gene transfer with improved patient clinical parameters. The Examiner has not provided any reason that similar genes delivered to similar tissues would not be expected to similarly improve patent clinical parameters. Removal of this rejection is requested.

Examiner's Indefiniteness Rejection:

Claims 57 and 63 were rejected for the [illegible] Applicants has clarified this term in newly presented claim 70. Removal of this rejection is requested.

Examiner's Novelty Rejection:
The Examiner rejected the prior pending claims as anticipated under 35 U.S.C. 102(e) by U.S. Patent 6,013,516 issued to Verma et al. To the extent this rejection may be applied to the newly presented claims, Applicant's respectfully traverse.

Stated more clearly in the new claims, the claimed invention is drawn to methods for the delivery of a heterologous gene to a target cell *in situ*. In contrast to the methods disclosed in the cited reference, the claimed invention requires a subject's cell to be converted into a replication-defective retroviral particle-producing cell that releases retroviral particles *in situ*, resulting in viral infection with gene delivery to neighboring target cells. The cited reference fails to teach or suggest such a method.

In contrast to the claimed invention, the cited reference discloses only the production and harvest of virus from producer cells, *in vitro*. Virus harvested from conditioned medium is used to infect non-producer cells. See, for example, the Summary of the Invention at Column 2, lines 25-36. A method for producing recombinant retrovirus is disclosed, including a final method step of "recovering the recombinant virus". The "recovered" virus is collected and used to infect cells.

The cited reference teaches "recovery" or "harvesting" of the produced recombinant retrovirus at every mention in the specification, and fails to even suggest the conversion of a subject's cell to a producer cell, or use of the subject's converted, viral particle-producing cell as the infection means. In contrast to the claimed method, the *in vivo* methods disclosed by this reference include transplantation of cells that had been infected with virus *ex vivo* or placement of virus directly into the central nervous system or ventricular cavities (see Column 8, lines 21-30). The reference fails to teach or suggest infection of target cells by virus produced *in situ* as required by the instant claims.

Accordingly, the cited reference fails to teach or suggest all the elements of the claimed method, and cannot anticipate the claims. Removal of this rejection is respectfully requested.

Conclusion:

Applicant's assert the claims are enabled by the specification, and are not taught or suggested by the cited prior art, as discussed above.

In light of the foregoing Amendment and Remarks, Applicants' assert the claims are in condition for allowance. Removal of all rejections and early notice of allowance is requested.

The Examiner is invited to telephone the undersigned attorney for clarification of any of these Remarks or Amendments, or to otherwise speed prosecution of this case.

Respectfully submitted,

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